DATA EVALUATION RECORD

FENAMIDONE

Study Type: §82-1a, 90-Day Oral Toxicity Study in Rats

Work Assignment No. 4-01-155D (MRIDs 45386025 & 45386023)

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DATA EVALUATION RECORD

STUDY TYPE: 90-Day Oral Toxicity [feeding] - rat; OPPTS 870.3100 [§82-1a]; OECD 408.

PC CODE: 046679 **DP BARCODE:** D278089
SUBMISSION NO.: S603761

TEST MATERIAL (PURITY): RPA 407213 (Fenamidone; 98.4% a.i.)

SYNONYMS: (S)-3,5-Dihydro-5-methyl-2-methylthio-5-phenyl-3-phenylamino-4H-imidazol-4-one

CITATION: Dange, M. (1995) Preliminary 90-Day Toxicity Study in the Rat by Dietary Administration. Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 94292, December 12, 1995. MRID 45386025. Unpublished.

Dange, M. (1995) 28-Day Toxicity Study in the Rat by Dietary Administration. Rhône-Poulenc Agrochimie, Centre de Recherche, Sophia Antipolis Cedex, France. Laboratory Study No.: SA 94120, April 7, 1995. MRID 45386023. Unpublished.

SPONSOR: Aventis CropScience, 2 T.W. Alexander Dr., Research Triangle Park, NC

EXECUTIVE SUMMARY: In a subchronic oral toxicity study (MRID 45386025), fenamidone (98.4% a.i., Lot/batch #LPO 185-2B) was administered to 10 Sprague Dawley rats/sex/group in the diet at dose levels of 0, 50, 150, 500, or 5000 ppm (equivalent to 0/0, 2.94/3.40, 8.95/10.55, 29.68/35.39, and 305.48/337.19 mg/kg bw/day). Food efficiency was not determined. There were no effects of treatment on mortality, ophthalmology, or urinalysis.

At 5000 ppm, **body weights** were decreased (decr. 9-12%; p<=0.05) compared to controls in the males from day 8 until study termination and in the females from day 64 until study termination. Body weight gains were decreased (p<=0.05) in the males during weeks 1, 12, and 13 and in the females during weeks 1 and 13. Overall (weeks 0-13) body weight gain (calculated by the

reviewers) was decreased in the males (decr. 22%) and females (decr. 28%) compared to controls. **Food consumption** was decreased (p<=0.05) in the males at week 1 (decr. 20%) and in the females at weeks 1, 3, 8-10, and 12 (decr. 10-18%). **Erythrocytes and hemoglobin** were slightly decreased (decr. 6-8%; p<=0.05) in the males and females. In the **spleens** of the males at this dose, enlargement (1/10 treated vs 0/10 controls) and increased incidences of prominent germinal centers (8/10 treated vs 2/10 controls) were observed. In the **liver** in the males, increased periportal vacuolation (7/10 treated vs 1/10 controls) and bile duct hyperplasia (5/10 treated vs 1/10 controls) were observed. Decreases (p<=0.05) in aspartate aminotransferase (decr. 40%) and alanine aminotransferase (decr. 46%) were observed in these animals. Glucose was decreased (p<=0.05) in the females (decr. 18%). Absolute, relative to body, and relative to brain weights of the **thymus** were decreased (decr. 26-34%; p<=0.05) in the males. Red area(s)/spot(s) on the thymus and thymus congestion were observed in the females (2/10 treated vs 0/10 controls). Absolute, relative to body, and relative to brain weights of the **thyroid** were increased (incr. 37-50%; p<=0.05) in the males.

The LOAEL for this study is 5000 ppm (equivalent to 305.48/337.19 mg/kg/day in males/females) based on decreased body weights, body weight gains, and food consumption in the males and females, enlargement and prominent germinal centers in the spleen in the males, and periportal vacuolation and bile duct hyperplasia in the liver in the males. The NOAEL is 500 ppm (equivalent to 29.68/35.39 mg/kg/day in males/females).

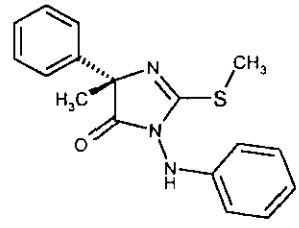
The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirements for a subchronic oral toxicity study in the rat (OPPTS 870.3100a; OECD 408).

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Flagging, and Quality Assurance statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: RPA 407213 (fenamidone)

Description:	White powder
Lot/Batch #:	LPO 185-2B
Purity:	98.4% a.i.
Compound Stability:	Stable in the diet for 3 weeks frozen followed by 1 week at room temperature
CAS #:	161326-34-7
Structure:	

2. Vehicle: Diet

3. Test animals:

Species:	Rat	
Strain:	Sprague Dawley	
Age/weight at study initiation:	6-7 weeks/ 256-299 g, males; 187-226 g, females	
Source:	Charles River France, St. Aubin-les-Elbeuf, France	
Housing:	Individually, in suspended, stainless steel, wire mesh cages	
Diet:	Certified rodent diet AO4C P1 (UAR, Villemoisson-sur-Orge, France), *ad libitum*, except during overnight fasting prior to blood and urine sampling.	
Water:	Filtered and softened tap water, *ad libitum*, except during overnight fasting prior to blood and urine sampling.	
Environmental conditions:	**Temperature:**	22 ± 2°C
	Humidity:	55 ± 15%
	Air changes:	10-15 per hour
	Photoperiod:	12 hours light/12 hours dark
Acclimation period:	14 days	

B. STUDY DESIGN

1. In life dates - Start: 10/19/94 End: 01/20/95

2. Animal assignment: Animals were selected from the middle of the weight range by an automatic procedure and were randomly assigned, stratified by weight, to the test groups presented in Table 1.

Table 1. Study design [a]

Test Group	Conc. in Diet (ppm)	Dose to Animal (mg/kg/day) M/F	# Males	# Females
Control	0	0/0	10	10
Low	50	2.94/3.40	10	10
Mid	150	8.95/10.55	10	10
Mid-High	500	29.68/35.39	10	10
High	5000	305.48/337.19	10	10

a Data were obtained from page 16 and Table 5 on page 61 of the study report (MRID 45386025).

3. **Dose selection rationale** - Based upon the results of a 28-day range-finding study (MRID 45386023) submitted with the 90-day study, the doses summarized in Table 1 were selected for the 90-day study. See Appendix in this DER for details of the 28-day study.

4. **Treatment preparation, administration, and analysis** - Test diets were prepared approximately every three weeks (4 preparations during the study) by adding the required quantity of finely ground test substance to the diet and dry mixing. Diet formulations were stored at -18°C until use. Homogeneity was verified for the 50 and 5000 ppm diets from each preparation during the study. Stability after being frozen for 3 weeks and then stored at room temperature for 1 week was determined for the 50 and 5000 ppm diets from the first preparation. Concentration analyses were determined for each dose level at each preparation during the study. All samples were analyzed in duplicate.

Results - Homogeneity Analysis (range as % of nominal):

50 ppm: 84-112% (except for one sample that was 78% which was mixed again and reanalyzed at 96%)
5000 ppm: 92-103%

Stability Analysis (% of nominal after 3 weeks frozen followed by 1 week at room temperature):

50 ppm: 87%
5000 ppm: 97%

Concentration Analysis (range as % of nominal):

50 ppm: 90-103%
150 ppm: 90-113% (except for one sample that was 129% which was mixed again and reanalyzed at 93%)
500 ppm: 81-96%
5000 ppm: 95-99%

The analytical data indicated that the mixing procedure was adequate and the variation between nominal and actual dosage to the animals was acceptable.

5. Statistics - The following statistical procedures were employed:

Parameter	Statistical Test
Body weights, body weight gains, and food consumption	Bartlett's test for homogeneity of variances followed by analysis of variance (ANOVA) and Dunnett's test if homogeneous variances or by Kruskal-Wallis and Mann-Whitney test if heterogeneous variances.
Hematology (except percentages and absolute values for eosinophils, basophils, and monocytes); clinical chemistry; urine pH, volume, and refractive index; and organ weights	Bartlett's test for homogeneity of variances followed by Dunnett's test if homogeneous variances or by Kruskal-Wallis and Mann-Whitney test if heterogeneous variances.

The levels denoting significance were $p \leq 0.05$ and $p \leq 0.01$ for each statistical comparison. In general, the statistical methods were considered appropriate. However, it was not stated that data were tested for normal distribution. This assumption should be verified before proceeding with parametric analyses.

C. METHODS

1. Observations - Animals were checked for mortality, moribundity, and clinical signs of toxicity twice daily (once daily on weekends and public holidays). Detailed physical examinations were performed at least weekly during the treatment period.

2. Body weight - Each rat was weighed prior to treatment, weekly throughout the study, and at termination. Group mean body weight gains were reported for each weekly interval during the study. Overall (weeks 0-13) body weight gains were calculated by the reviewers from the group mean body weight data.

3. *Food consumption, food efficiency, and compound intake* - Food consumption (g) was recorded weekly for each rat. Food efficiency was not calculated. Group mean achieved test substance intake (mg/kg/day) was calculated for each week and for the overall (weeks 1-13) study.

4. Ophthalmoscopic examination - The eyes of each animal were examined by indirect ophthalmoscopy prior to treatment. *Animals in the control and 5000 ppm groups were examined* during study week 13.

5. Hematology & clinical chemistry - Blood was collected from the retro-orbital venous plexus of each rat during week 13. Animals were fasted overnight prior to blood sampling and were anesthetized by inhalation of ether. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc. (MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*		
	(*Activated partial thromboplastin time*)		
	(Clotting time)		
X	(Prothrombin time)		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin*
X	Chloride	X	Creatinine*
	Magnesium	X	Urea nitrogen*
X	Phosphate	X	Total cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
		X	Total bilirubin
	ENZYMES	X	Total protein (TP)*
X	Alkaline phosphatase (ALK)*	X	Triglycerides
	Cholinesterase (ChE)		Serum protein electrophores
	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/also SGPT)*		
X	Aspartate aminotransferase (AST/also SGOT)*		
	Sorbitol dehydrogenase*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for 90-day oral rodent studies based on Guideline 870.3100

6. Urinalysis[1] - Urine was collected overnight from each surviving rat prior to sacrifice during study week 14. Food and water were withheld from animals during overnight urine collection. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose
X	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood/blood cells*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

I Optional for 90-day oral rodent studies based on Guideline 870.3100
* Recommended for 90-day oral rodent studies based on Guideline 870.3100

7. **Sacrifice and pathology** - During week 14, all animals were fasted overnight, euthanized by exsanguination under pentobarbital anesthesia, and were subjected to a gross pathological examination. The CHECKED (X) tissues were collected, preserved in 10% neutral buffered formalin (except eyes, Harderian gland, epididymis, and testis which were fixed in Davidson's fixative), and stained with hematoxylin and eosin. The (XX) organs were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta*	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Peripheral nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	XX	Pituitary*
X	Duodenum*	XX	Spleen*+	X	Eyes (optic nerve)*
X	Jejunum*	XX	Thymus*+		GLANDULAR
X	Ileum*			XX	Adrenal gland*+
X	Cecum*		UROGENITAL	X	Lacrimal gland
X	Colon*	XX	Kidneys*+	XX	Parathyroid*
X	Rectum*	X	Urinary bladder*	XX	Thyroids*
XX	Liver*+	XX	Testes*+		OTHER
	Gall bladder (not rat)*	XX	Epididymides*+	X	Bone (sternum and/or femur)
	Bile duct (rat)	XX	Prostate*	X	Skeletal muscle
X	Pancreas*	X	Seminal vesicles*	X	Skin*
	RESPIRATORY	XX	Ovaries*+	X	All gross lesions and masses*
X	Trachea*	XX	Uterus*+		
X	Lung*	X	Mammary gland*		
	Nose*	X	Vagina		
	Pharynx*				
X	Larynx*				

* Recommended for 90-day oral rodent studies based on Guideline 870.3100
\+ Organ weights required for rodent studies.

Microscopic examination was performed on all tissues (except the larynx) collected from animals in the control and 5000 ppm groups. Tissues from the liver, lungs, kidneys, and any gross lesions were also examined in the intermediate dose groups. Additionally, if a pathological effect was established at 5000 ppm, target tissues from the intermediate dose groups were examined.

II. RESULTS

A. OBSERVATIONS

1. **Clinical signs of toxicity** - There were no treatment-related clinical observations in the males. The number of rats that showed irritability to touch were dose-dependently increased in the 500 ppm (2/10 treated vs 0/10 controls) and 5000 ppm (5/10 treated vs 0/10 controls) females. However, this behavior was considered not to be of toxicological importance because the frequency was minimal; all 7 animals exhibited this behavior on study day 90 only. There were no other clinical observations that could be attributed to treatment.

2. **Mortality** - There were no unscheduled deaths during the study.

B. BODY WEIGHT AND WEIGHT GAIN: Body weights were decreased (↓9-12%; $p \leq 0.05$) at 5000 ppm in the males from day 8 until study termination and in the females from day 64 until study termination (Table 2a). Body weight gains were decreased (↓48-211%; $p \leq 0.05$) in the 5000 ppm males during weeks 1, 12, and 13 and in the females during weeks 1 and 12 (Table 2b). Body weight gains were also decreased ($p \leq 0.05$) in the 150 ppm females during week 1, in the 150 ppm males during week 2, and in the 500 ppm males and females during week 12; however, these differences were considered unrelated to treatment because they were sporadic and did not result in significantly decreased body weights. Overall (weeks 0-13) body weight gain (calculated by the reviewers) was decreased in the 5000 ppm males (↓22%) and females (↓28%) compared to controls (Table 2a).

Table 2a. Mean (± SD) body weights and overall body weight gains (g) in rats treated with fenamidone in the diet for up to 90 days.[a]

Study Day	Dose (ppm)				
	0	50	150	500	5000
Males					
1	273.4 ± 8.8	275.4 ± 9.2	278.7 ± 9.5	280.3 ± 12.0	276.6 ± 10.5
8	335.5 ± 18.6	342.5 ± 13.6	340.6 ± 11.7	338.3 ± 18.0	309.2 ± 14.1** (↓9)
90	646.9 ± 46.7	639.0 ± 50.6	622.1 ± 46.0	625.2 ± 65.2	566.6 ± 30.9** (↓12)
Overall (1-90) gain[b]	373.5	363.6	343.4	344.9	290.0 (↓22)
Females					
1	203.8 ± 9.6	201.2 ± 9.4	203.5 ± 11.4	204.5 ± 10.1	204.6 ± 9.3
64	312.2 ± 19.9	306.2 ± 14.7	312.5 ± 22.6	306.7 ± 25.8	282.9 ± 22.0* (↓9)
90	331.5 ± 23.9	314.8 ± 16.8	324.7 ± 22.6	326.9 ± 31.8	296.0 ± 18.7** (↓11)
Overall (1-90) gain[b]	127.7	113.6	121.2	122.4	91.4 (↓28)

a Data were obtained from Table 2 on pages 43-47 of the study report (MRID 45386025); n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.
b Calculated by the reviewers from the group mean body weight data.
* Significantly different from the control group at $p \leq 0.05$.
** Significantly different from the control group at $p \leq 0.01$.

Table 2b. Mean (± SD) body weight gains (g) in rats treated with fenamidone in the diet for up to 90 days.[a]

Interval (days)	Dose (ppm)				
	0	50	150	500	5000
Males					
1-8	8.87 ± 2.08	9.58 ± 1.21	8.84 ± 1.54	8.28 ± 1.58	4.65 ± 1.58** (↓48)
8-15	8.38 ± 2.21	7.75 ± 1.29	6.11 ± 1.23**	6.54 ± 2.66	6.95 ± 0.96
78-84	2.45 ± 1.54	2.45 ± 2.16	1.58 ± 1.34	0.88 ± 1.16*	0.76 ± 0.76** (↓69)
84-90	1.28 ± 1.55	1.00 ± 0.75	1.50 ± 0.68	0.63 ± 1.14	-0.41 ± 1.51* (↓132)
Females					
1-8	2.64 ± 0.68	3.17 ± 1.07	3.15 ± 0.41*	2.65 ± 1.25	1.71 ± 1.30* (↓35)
78-84	0.61 ± 0.85	0.26 ± 1.08	0.51 ± 1.58	-0.71 ± 1.06*	-0.68* ± 0.85 (↓211)

a Data were obtained from Table 3 on pages 48-54 of the study report (MRID 45386025); n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from the control group at $p \leq 0.05$.
** Significantly different from the control group at $p \leq 0.01$.

C. FOOD CONSUMPTION

1. Food consumption - Group mean weekly food consumption decreased ($p \leq 0.05$) in the 5000 ppm males at week 1 (↓20%) and in the 5000 ppm females at weeks 1, 3, 8-10, and 12 (↓10-18%; Table 3). With the exception of an incidental decrease ($p \leq 0.05$) in the 50 ppm females at week 10 (↓12%), food consumption in all other treated groups was comparable to controls for males and females.

Table 3. Mean (± SD) food consumption (g) in rats treated with fenamidone in the diet for up to 90 days.[a]

Study Week	Dose (ppm)				
	0	50	150	500	5000
Males					
1	30.0 ± 2.2	30.5 ± 2.3	29.8 ± 1.9	29.9 ± 3.1	24.1 ± 2.7** (↓20)
Females					
1	19.0 ± 1.0	19.3 ± 1.3	20.0 ± 1.3	19.6 ± 1.6	15.6 ± 1.9** (↓18)
3	20.5 ± 2.1	19.4 ± 1.1	20.4 ± 1.6	19.8 ± 1.9	18.4 ± 1.2* (↓10)

a Data were obtained from Table 4 on pages 55-59 of the study report (MRID 45386025); n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from the control group at $p \leq 0.05$.
** Significantly different from the control group at $p \leq 0.01$.

2. Compound consumption - Group mean compound intake values (mg/kg/day) for the overall study are reported in Table 1.

3. Food efficiency - Food efficiency was not determined.

D. OPHTHALMOSCOPIC EXAMINATION: The Sponsor stated that no ophthalmological abnormalities were observed in the control or 5000 ppm males or females; however, neither summary nor individual data were provided.

E. BLOOD ANALYSES

1. Hematology - Erythrocytes and hemoglobin were decreased (↓6-8%; $p \leq 0.05$) in the 5000 ppm males and females (Table 4).

Table 4. Selected mean (± SD) hematological findings in rats treated with fenamidone in the diet for up to 90 days.[a]

Hematological Parameter	Dose (ppm)				
	0	50	150	500	5000
Males					
Erythrocytes (10^{12}/L)	9.01 ± 0.30	9.20 ± 0.42	9.20 ± 0.35	9.08 ± 0.45	8.48 ± 0.29* (↓6)
Hemoglobin (g/100mL)	15.4 ± 0.4	15.4 ± 0.4	15.7 ± 0.6	15.5 ± 0.3	14.5 ± 0.3** (↓6)
Females					
Erythrocytes (10^{12}/L)	8.32 ± 0.42	8.39 ± 0.33	8.41 ± 0.46	8.45 ± 0.44	7.69 ± 0.30** (↓8)
Hemoglobin (g/100mL)	15.0 ± 0.7	15.2 ± 0.2	15.2 ± 0.4	15.2 ± 0.5	14.0 ± 0.4** (↓7)

a Data were obtained from Table 6 on pages 62-68 of the study report (MRID 45386025); n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from the control group at $p \leq 0.05$.
** Significantly different from the control group at $p \leq 0.01$.

2. <u>Clinical chemistry</u> - In the 5000 ppm males, decreases ($p \leq 0.05$) were observed in aspartate aminotransferase (↓40%) and alanine aminotransferase (↓46%; Table 5). Glucose was decreased ($p \leq 0.05$) in the 5000 ppm females (↓18%).

Table 5. Selected mean (± SD) clinical chemistry findings in rats treated with fenamidone in the diet for up to 90 days.[a]

Clinical Chemistry Parameter	Dose (ppm)				
	0	50	150	500	5000
Males					
Aspartate aminotransferase (IU/L)	70 ± 48	57 ± 13	66 ± 34	49 ± 9	42 ± 8** (↓40)
Alanine aminotransferase (IU/L)	39 ± 36	28 ± 5	29 ± 11	23 ± 4* (↓41)	21 ± 9* (↓46)
Females					
Glucose (mmol/L)	9.38 ± 1.93	8.43 ± 0.82	8.92 ± 0.83	8.54 ± 0.78	7.72 ± 0.81* (↓18)

a Data were obtained from Table 7 on pages 69-77 of the study report (MRID 45386025); n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.
* Significantly different from the control group at $p \leq 0.05$.
** Significantly different from the control group at $p \leq 0.01$.

F. <u>URINALYSIS</u>: There were no treatment-related effects on urinalysis.

G. SACRIFICE AND PATHOLOGY

1. **Organ weight** - Absolute, relative to body, and relative to brain weights of the thymus were decreased (↓26-34%; p≤0.05) in the 5000 ppm males (Table 6). Absolute, relative to body, and relative to brain weights of the thyroid were increased (↑37-50%; p≤0.05) in these animals. Additionally, at 5000 ppm, the following relative (to body weight) organ weights were increased: (i) brain and liver in the males and females (↑11-19%); (ii) spleen, adrenal, and thyroid in the females (↑26-33%); and (iii) kidney in the males (↑13%). However, the absolute weights of these organs and their weights relative to brain weight were comparable to controls; therefore, these increases were considered to be due to the decreased body weights in the 5000 ppm animals. All other organ weights were comparable to controls.

Table 6. Selected mean (± SD) organ weights in male rats treated with fenamidone in the diet for up to 90 days.[a]

Organ	Dose (ppm)				
	0	50	150	500	5000
Thymus					
absolute (g)	0.604 ± 0.184	0.556 ± 0.107	0.585 ± 0.133	0.502 ± 0.166	0.397 ± 0.072** (↓34)
relative to body (%)	0.098 ± 0.028	0.091 ± 0.015	0.098 ± 0.018	0.086 ± 0.032	0.073 ± 0.013* (↓26)
relative to brain (%)	27.01 ± 8.28	25.55 ± 5.04	26.34 ± 6.01	22.90 ± 8.12	17.90 ± 3.27** (↓34)
Thyroid					
absolute (g)	0.027 ± 0.005	0.024 ± 0.002	0.026 ± 0.007	0.030 ± 0.009	0.037 ± 0.011** (↑37)
relative to body (%)	0.004 ± 0.000	0.004 ± 0.000	0.004 ± 0.001	0.005 ± 0.001	0.006 ± 0.001** (↑50)
relative to brain (%)	1.240 ± 0.253	1.135 ± 0.151	1.179 ± 0.299	1.383 ± 0.420	1.713 ± 0.517** (↑38)

a Data were obtained from Tables 11 through 13 on pages 87-101 of the study report (MRID 45386025); n=10. Percent difference from controls, calculated by the reviewers, is included in parentheses.

* Significantly different from the control group at p≤0.05.

** Significantly different from the control group at p≤0.01.

2. **Gross pathology** - At 5000 ppm, spleen enlargement was noted in the males (1/10 treated vs 0/10 controls), and red area(s)/spot(s) on the thymus were observed in the females (2/10 treated vs 0/10 controls; Table 7). Additionally, the following dose-dependent findings were noted in the males (1/10 each treated vs 0/10 controls), but were uncorroborated by histopathology and were considered incidental: (i) small prostate at 5000 ppm; (ii) enlarged liver at 5000 ppm; and (iii) whitish pigmentation of the kidney at 500 and 5000 ppm. There were no other dose-dependent macroscopic observations.

Table 7. Selected gross pathological findings (# affected) in rats treated with fenamidone in the diet for up to 90 days.[a]

Gross Observation	Dose (ppm)				
	0	50	150	500	5000
Males					
Spleen - enlarged	0	0	0	0	1
Females					
Thymus - red area(s)/spot(s)	0	0	0	0	2

a Data were obtained from Table 14 on pages 102-104 of the study report (MRID 45386025); n=10.

3. **Microscopic pathology** - In the 5000 ppm males, increased periportal vacuolation (7/10 treated vs 1/10 controls) and bile duct hyperplasia (5/10 treated vs 1/10 controls) were observed in the liver, and increased prominent germinal centers were found in the spleen (Table 8). In the 5000 ppm females, thymus congestion was noted (2/10 treated vs 0/10 controls). Several other dose-dependent findings were noted, such as mononuclear cell infiltration in the kidney and unilateral atrophy of the testes and epididymis; however, these observations were considered unrelated to treatment because they were incidental and/or minor in severity.

Table 8. Selected microscopic findings (# affected) in rats treated with fenamidone in the diet for up to 90 days.[a]

Microscopic Observation	Dose (ppm)				
	0	50	150	500	5000
Males					
Liver					
Increased periportal macro/micro-vacuolation	1	0	1	0	7
Bile duct hyperplasia	1	0	0	0	5
Spleen					
White pulp, prominent germinal centers	2	0	0	0	8
Females					
Thymus					
Congestion	0	0	0	0	2

a Data were obtained from Table 15 on pages 105-107 of the study report (MRID 45386025); n=10.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS: It was concluded that the NOAEL was 500 ppm based on decreased body weights, body weight gains, food consumption, and a slight decrease in red blood cell parameters at 5000 ppm. No meaningful changes attributable to treatment were observed in clinical chemistry, ophthalmology, urinalysis, organ weights, gross pathology, or histopathology.

B. REVIEWER COMMENTS: There were no effects of treatment on mortality, ophthalmology, or urinalysis.

At 5000 ppm, body weights were decreased (↓9-12%; $p \leq 0.05$) in the males from day 8 until study termination and in the females from day 64 until study termination. Body weight gains were decreased (↓48-211%; $p \leq 0.05$) in the males during weeks 1, 12, and 13 and in the females during weeks 1 and 12. Overall (weeks 0-13) body weight gains (calculated by the reviewers) were decreased in the males (↓22%) and females (↓28%) compared to controls. Food consumption was decreased ($p \leq 0.05$) in the males at week 1 (↓20%) and in the females at weeks 1, 3, 8-10, and 12 (↓10-18%).

Erythrocytes and hemoglobin were decreased (↓6-8%; $p \leq 0.05$) in the 5000 ppm males and females. These changes were considered treatment-related; however, they were considered toxicologically unimportant because they were minor.

Increased periportal vacuolation (7/10 treated vs 1/10 controls) and bile duct hyperplasia (5/10 treated vs 1/10 controls) indicated a mild effect of treatment on the liver in the 5000 ppm males. Aspartate aminotransferase (↓40%) and alanine aminotransferase (↓46%) were decreased ($p \leq 0.05$) in these animals; the toxicological significance of these decreases is uncertain. Glucose was decreased ($p \leq 0.05$) in the 5000 ppm females (↓18%). The Sponsor stated that these clinical chemistry findings were representative of the usual background pathology in this strain of rat; however, historical control data were not provided.

At 5000 ppm, absolute, relative to body, and relative to brain weights of the thymus were decreased (↓26-34%; $p \leq 0.05$) in the males. Red area(s)/spot(s) on the thymus and thymic congestion were observed in the females (2/10 treated vs 0/10 controls). Absolute, relative to body, and relative to brain weights of the thyroid were increased (↑37-50%; $p \leq 0.05$) in the males at this dose; however, no histopathological changes were observed in this organ. In the spleen in the males at this dose, enlargement (1/10 treated vs 0/10 controls) and increased incidences of prominent germinal centers (8/10 treated vs 2/10 controls) were observed. The Sponsor stated that these findings fell within the usual background pathology in this strain of rat; however, in the absence of historical control data, they are considered treatment-related.

The LOAEL for this study is 5000 ppm (equivalent to 305.48/337.19 mg/kg/day in males/females) based on decreased body weights, body weight gains, and food consumption in the males and females, enlargement and prominent germinal centers in the spleen in the males, and periportal vacuolation and bile duct hyperplasia in the liver in the males. The NOAEL is 500 ppm (equivalent to 29.68/35.39 mg/kg/day in males/females).

The submitted study is classified as **acceptable/guideline** and satisfies the guideline requirements for a subchronic oral toxicity study in the rat (OPPTS 870.3100a; OECD 408).

C. **STUDY DEFICIENCIES:** The following minor deficiencies were noted, but do not change the conclusions of this DER:

- Sorbitol dehydrogenase and gamma glutamyl transferase were not measured.
- The nose and pharynx were not examined microscopically at sacrifice.